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10/766,755	01/28/2004	Gregory L. Stahl	A0752.70001US01	2264

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EXAMINER

HADDAD, MAHER M

ART UNIT	PAPER NUMBER
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1644

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/766,755	Applicant(s) STAHL ET AL.	
	Examiner Maher M. Haddad	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 November 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13, 15-17, 22-33, 35-38, 40-51, 53-62 and 67-74 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13, 15-17, 22-33, 35-38, 40-51, 53-62 and 67-74 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>05/13/2009</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. Claims 1-13, 15-17, 22-33, 35-38, 40-51, 53-62 and 67-74 are pending and under examination.
2. The first paragraph of the specification should be amended to reflect the status of parent application No. 09/464,303, “now US. Pat. 7,273,925”.
3. Applicant’s IDS, filed 05/13/2009, is acknowledged, however, the Janeway references with the page numbers were crossed out because the date of the publication is not listed. Applicant is invited to provide the date of publication for the Janeway references.
4. The Stahl declaration under 37 C.F.R. § 1.132 in conjunction with the ATCC deposit information, filed 02/11/2002 in parent Applicant 09/464,303, now US. Pat. 7,273,925 are sufficient to satisfy the deposit of biological materials 3F8 (HB-12621), 2A9 (HB-12621), and hMBL1.2 (HB-12620)hybridoma, under 35 U.S.C. § 112, first paragraph.
5. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
6. Claims 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
 - A. The “mammalian cell with a surface exposed MBL ligand” recited in claim 12 has no antecedent basis in base claim 1.
7. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
8. Claims 1-13, 15-17, 22-33, 35-38, 40-51, 53-62 and 67-74 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite “the MBL inhibitor is a peptide, protein, or antibody or antigen-binding fragment thereof” as part of the invention.

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However, neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (a peptide, protein, or antibody or antigen-binding fragment thereof) to describe the claimed genus, nor does it provide a description of structural features that are common to species (a peptide, protein, or antibody or antigen-binding fragment thereof). The specification provides no structural description of a peptide, protein, or antibody or antigen-binding fragment thereof other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed a peptide, protein, or antibody or antigen-binding fragment thereof looks like. The specification's disclosure is inadequate to describe the claimed genus of a peptide, protein, or antibody or antigen-binding fragment thereof.

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. However, a generic statement such as a peptide, protein, or antibody or antigen-binding fragment thereof" is not an adequate written description of the genus because it does not distinguish the claimed genus from others. It does not specifically define any of the peptides, proteins and antibodies that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate. "). There are insufficient relevant identifying characteristics disclosed.

U.S. Patent 7,211,396 teaches that human MBL gene (mbl2) shows a number of allelic variants. Some occur in the promoter region, the two most significant occurring at positions -550 (H or L) and -221 (Y or X); a further variant occurs in the 5'-untranslated region at position +4 (P or Q); and three occur in exon 1, at position +223 (A or D, Arg52Cys), +230 (A or B, Gly54Asp) and +239 (A or C, Gly57Glu). The promoter haplotypes HY, LY and LX are associated with high, medium and low plasma levels of MBL, respectively, whereas the haplotypes of exon 1 affect the structure and association of the protein chains. Among A/A genotypes (i.e. with a normal collagenous region), only the LXP/LXP genotypes showed low plasma MBL levels. A/B, A/C and A/D genotypes (i.e. heterozygous for normal and abnormal collagenous regions) showed reduced plasma MBL levels as determined by the old method described; when this was combined with an LX haplotype, even lower levels were recorded. B/B, C/D and D/D genotypes (i.e. with an anomaly of all collagenous regions) showed very low levels of MBL as determined by the old method, even though none of these subjects showed an LX haplotype. The frequencies

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of the exon 1 haplotypes A, B, C and D in the Danish donors were 0.76, 0.135, 0.020 and 0.085, respectively. This means that the frequencies of A/A, B/B, C/C and D/D genotypes will be the square of these, i.e. affecting 58.76%, 1.82%, 0.04% and 0.72% of the population, respectively.

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention, the peptide, protein, antibody or antigen-binding fragment thereof and its MBL inhibition function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of peptides, proteins, antibodies, and antigen-binding fragment thereof which retain the features essential to the instant invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See Vas-Cath at page 1116.) Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 “Written Description” Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

9. Claims 1-13, 15-17, 22-33, 35-38, 40-51, 53-62 and 67-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

At issue whether the specification is enabled for a method for inhibiting lectin complement pathway (LCP) associated complement activation with MBL inhibitor such as a peptide, protein,

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antibody or antigen-binding fragment thereof in claims 1 and 40, wherein the LCP associated complement activation mediates a cellular injury in claim 2, contributes to tissue injury associated with atherosclerosis in claims 3 and 41, contributes to tissue injury associated with the pulmonary system in claims 4 and 42, wherein the cellular injury mediated by LCP associated complement activation contributes to tissue injury associated with arthritis, myocardial infarction, ischemia, reperfusion, transplantation, cardiopulmonary bypass (CPB), stroke, acute respiratory distress syndrome (ARDS), systemic lupus erythematosus (SLE), Lupus, or dialysis in claims 6-7 and 44-45, the method further comprising administering to the subject any "therapeutic treatment" for treating an "MBL mediated disorder" associated with the cellular injury mediated by LCP associated complement activation in claims 8 and 46, wherein the therapeutic treatment is any "drug" in claims 9 and 47, or comprises revascularizing a coronary artery in claims 10 and 48, wherein the MBL inhibitor binds MBL in claims 13 and 50, binds to a human MBL epitope in claims 15 and 57, any antigen-binding fragment of any antibody in claim 22, such as the one recited in claim 23, any antibody in claims 25 and 70, any monoclonal antibody in claims 26 and 71, inhibits C3b deposition in claims 30 and 60, is any "MBL binding peptide, protein, or antibody or antigen binding fragment thereof, and inhibits C3b deposition with an EC₅₀ of between 10⁻⁹ to 10⁻⁷ mol/L in claims 31 and 61, binds to any MASP or mannan in claim 33. wherein the antibody is monoclonal, a single-chain antibody, humanized antibody in claims 28-29, 35-37, 53-55, 67-68 and 73-74, wherein MASP is MASP-1 or MASP-2 in claims 38 and 56, wherein the MBL inhibitor inhibits MBL deposition on a mammalian cell with a surface exposed MBL ligand in claim 50, wherein the MBL inhibitor binds MBL, MASP or Mannan in claim 51.

The specification discloses that oxidative stress of human endothelial cells *in vitro* leads to MBL deposition and LCP activation. Further, dual labeling for MBL and C3 deposition on normoxic and hypoxic HUVECs was performed to demonstrate co-localization of these complement components and MBL-dependent complement pathway activation. Moreover, the specification demonstrates that functional inhibition of MBL with a mAb attenuates C3 deposition following oxidative stress of human endothelial cells (see Example 9 pages 47-48). Figure 4a shows that inhibition of iC3b deposition with D-mannose or GlcNAc did not significantly affect iC3b deposition after endothelial oxidative stress. Figure 4b shows that MBL-depleted human serum show less iC3b deposition in the reoxygenated hypoxic HUVECs. On the basis of the disclosed apparent *in vitro* observation alone, applicant concludes that the scope of the MBL inhibitors such as any peptide, protein, or antibody or antigen-binding fragment thereof can have biological activity to inhibiting lectin complement pathway associated complement activation and be provided as pharmaceutical compositions to subjects including human to effectively inhibit LCP associated complement activation mediated a cellular injury, tissue injury.

At issue the generic method of inhibiting lectin complement pathway (LCP) associated complement activation with MBL inhibitors. The Examiner notes that the method encompasses inhibiting dysfunctional lectin pathway as a result of MASP-1, MASP-2, C2, C3, C4 genetic deficiencies or dysfunction, however, it cannot be seen how the MBL inhibitors would result in inhibiting dysfunctional lectin pathway as a result of MASP-1, MASP-2, C2, C3, C4 genetic deficiencies or dysfunction. Indeed, according to Fig. 1 of the specification, all these molecules

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are downstream of the MBL in the lectin complement pathway associated complement activation. Yet, Applicant is claiming that MBL inhibitors can be the magic bullet against all lectin complement pathway associated complement activation.

The influence of a scientific theory should depend on its empirical and demonstrable aspects and not its underlying logic. Yet such empirical and demonstrable aspects of the claimed method of treating atherosclerosis, pulmonary system, arthritis, myocardial infraction, ischemia, reperfusion, transplantation, cardiopulmonary bypass (CPB), stroke, acute respiratory distress syndrome (ARDS), systemic lupus erythematosus (SLE) lupus, or dialysis with the MBL inhibitor are lacked in the instant specification. No working empirical data demonstrating that the MBL inhibitors such as anti-MBL antibody would treat atherosclerosis, pulmonary system, arthritis, myocardial infraction, ischemia, reperfusion, transplantation, cardiopulmonary bypass (CPB), stroke, acute respiratory distress syndrome (ARDS), systemic lupus erythematosus (SLE) lupus, or dialysis is disclosed. Stanworth et al (British Journal of Rheumatology, 1998, 57:186-188) teach that no evidence was found to support an association between the presence of MBL allele and protection from rheumatoid disease, genotype frequencies were similar in both groups. This suggests that complement activation via MBL-aglactosyl IgG complexes is unlikely to play a major role in the pathophysiology of RA (see abstract in particular).

The specification does not teach how to extrapolate data obtained from in a cell-based assay to the development of effective in vivo mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the MBL inhibitors exemplified in the specification.

Applicant has not provided sufficient biochemical information that distinctly identifies MBL inhibitor such as any "peptide, protein, or antibody or antigen-binding fragment thereof" that binds to "mammalian cell with a surface exposed MBL ligand", "binds to MBL", "binds to a human MBL epitope", "inhibits VCAM-1 expression" and "binds to MASP or mannan". While any MBL inhibitor may have some notion of the activity of the "inhibitory agent", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention. The specification fails to provide any guidance on how to make any MBL inhibitor peptide, protein, antibody that can be used to inhibit adhesion cellular injury in a subject.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Applicant has not enabled structurally related and unrelated compounds comprising any MBL inhibitor "peptide, protein or antibody" which would be expected to have difference in their activities. There is insufficient direction or objective evidence as to how to make and to how to use any peptide, protein or antibody, which inhibits any MBL for the number of possibilities associated with the myriad of direct and indirect effects associated with various molecules and, in turn, as to whether such a desired effect can be

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achieved or predicted, as encompassed by the claims. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the specific structure of the MBL inhibitor such as specific peptide, protein, or antibody and still provide or maintain sufficient or the claimed activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

It is recognized in the art that ligand must possess significant structural and chemical complementarity to their target receptors (Kuntz, Science, 1992, Vol. 257:1078-1082, especially page 10709, 2nd col., lines 1-4 and 9-12 under heading "Structure-Based Design") and that ligands generally bind to native states of proteins with little or no interaction with unfolded states (Miller et al, Protein Science, 1997, 6:2166-2179, especially page 2166, 2nd col., lines 18-20) and further that alterations in protein structure lead to alterations in bindings affinity proportional to the magnitude of the alteration (Miller et al, abstract, lines 2-4). Finally, Kuntz teaches that as little as 2% of compounds predicted to inhibit specific enzymatic or receptor systems actually shown inhibition in the micromolar range (page 1080, 3rd col.). The claims encompass yet to be identify MBL inhibitors. Collard et al teach (*American Journal of Pathology*. 2000;156:1549-1556. IDS reference) teaches that potent, selective inhibitors of the LCP have not yet been described (see introduction 2nd ¶, page 1549). To date, we have not been able to generate a functionally inhibitory antibody to rat MBL. This difficulty may be due to the presence of two rat MBL isoforms (see page 1555, 2nd col., 1st full ¶).

Cochlovius *et al* (Modern Drug Discovery, 2003, pages 33-34 and 3738) teach that therapeutic antibodies after years of promise, magic bullets appear to be on the upswing. Cochlovius et al teach that in contrast to *in vitro* models, and partly animal-human xenograft systems, tissue cells *in vivo* seems to express molecules for defense against cellular immune systems as well as against complement. Although these defense mechanisms are still poorly understood, they provide some hints as to why many potential therapeutics perform marvelously *in vitro* but a fairly high portion of them still fail *in vivo* (see page 37, under The Cancer Market). Thus, it is not clear that reliance on the *in vitro* studies accurately reflects the relative mammal and human efficacy of the claimed therapeutic strategy. The specification does not teach how to extrapolate data obtained from *in vitro* studies to the development of effective *in vivo* mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of any antibody or antigen-binding fragment thereof, including anti-MBL antibodies, by administering to a subject a therapeutically effective amount of therapeutic composition. Thus in the absence of working examples or detailed guidance in the specification, the uses of any therapeutic composition comprising the anti-MBL antibody are fraught with uncertainties. It is not enough to rely on *in vitro* studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to use in humans or animals. *Ex parte Maas*, 9 USPQ2d 1746. There must be a rigorous correlation of pharmacological activity between the disclosed *in vitro* use and an *in vivo* use to establish practical therapeutic use.

Given the relatively incomplete understanding in correlating *in vitro* assays and *in vivo* animal

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models to clinical treatment of lectin complement pathway associated complement activation mediates a cellular/tissue injury involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims, the claims are not enabled. See MPEP 2164.08.

If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied. "The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements...However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims." MPEP § 2164.03.

"Substantiating evidence may be in the form of animal tests which constitute recognized screening procedures with clear relevance to utility in humans. See *Ex parte Krepelka*, 231 USPQ 746 (Board of Patent Appeals and Interferences 1986) and cases cited therein." *Ex parte Maas*, 9 USPQ2d 1746.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) *the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

11. Claims 1-2, 12, 30-33, 38, 40, 50, 51, 56 and 60-62 are rejected under 35 U.S.C. 102(b) as being anticipated by US. Pat. No. 5,270,199 (IDS reference A1).

The '199 patent teaches the use of mannose binding protein (MBP, or MBL) MBP-human and related peptides (a protein or a peptide) can be administered by routine methods in pharmaceutically acceptable carrier substances. They can be injected directly into the blood stream of an animal. The '199 patent teaches that the MBP-human or related peptides can be administered to prevent infection in immunocompromised patients (e.g., cancer patients subjected to long term intravenous chemotherapy (i.e., cellular injury)) (see col., 10, line 13+). Therefore, it is clear that both '199 patent and applicant administer the same composition comprising the same protein or peptide to the same patient to achieve the same results. The prior art and applicant have suggested different mechanisms. It is acknowledged that applicant now

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recites and believes in a different mechanism of action than the prior art. However, the instant methods do not negate or preclude the mechanism of action indicated by the prior art nor does applicant provide objective evidence to distinguish the prior art from the claimed invention.

While the prior art disclosure may be silent as to the “inhibiting LCP associated complement activation” per se; ; the instant claims merely recite newly discovered results of “inhibiting LCP associated complement” of a known method of treating the same patients with the MBL inhibitor. The claim language is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims. The recitation of “effective amounts” statement of the intended results of administering those amounts does not change those amounts or otherwise limit the claim. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 00-1304 (CAFC 4/20/01)

The prior art MBP protein and related peptides would bind to MASP in the absence of evidence to the contrary. The claimed function limitations are inherent properties.

The reference teachings anticipate the claimed invention.

12. Claims 1-2, 12, 30-33, 38, 40, 50, 51, 56 and 60-62 rejected under 35 U.S.C. 102(b) as being anticipated by Fischer et al (Scand. J. Immunol. 39,439-445, 1994).

Fischer et al teach that four week-old BALB/c mice were injected subcutaneously with 50 µg human MBP 1 day before intravenous infection with herpes simplex virus type 2 (HSV-2). Fischer et al teach that a three-fold increase in virus titre of the liver was observe on day 3 of the infection in the mice pretreated with the MPB, whereas no effect was seen on days 1 and 5 (see abstract). Fischer et al concluded that the collectins mannan-binding protein may provide HSV-2 with an alternative port of entry into cells leading to infection enhancement (cellular injury) (see abstract and page 444, last ¶).

Therefore, it is clear that both Fischer et al and applicant administer the same composition comprising the same protein or peptide to the same patient to achieve the same results. The prior art and applicant have suggested different mechanisms. It is acknowledged that applicant now recites and believes in a different mechanism of action than the prior art. However, the instant methods do not negate or preclude the mechanism of action indicated by the prior art nor does applicant provide objective evidence to distinguish the prior art from the claimed invention.

While the prior art disclosure may be silent as to the “inhibiting LCP associated complement activation” per se; ; the instant claims merely recite newly discovered results of “inhibiting LCP associated complement” of a known method of treating the same patients with the MBL inhibitor. The claim language is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims. The recitation of “effective amounts” statement of the intended results of administering those amounts does not change those amounts or otherwise limit the claim. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 00-1304 (CAFC 4/20/01)

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The prior art MBP protein and related peptides would bind to MASP in the absence of evidence to the contrary. The claimed function limitations are inherent properties.

The reference teachings anticipate the claimed invention.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-2, 6, 12, 13, 15, 25, 26, 30-33, 35, 38, 40, 44, 50, 51, 53, 56, 57, 60-63, 70-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Endo et al (Nephrol Dial Transplant. 1998 Aug;13(8):1984-90, IDS C13).

Endo et al teach glomerular deposition of MBL indicates a novel mechanism of complement activation in IgA nephropathy (kidney disease that requires dialysis). Endo et al teach that recent studies have shown that MBL initiates activation of complement cascade (lectin pathway) utilizing two types of MBP-associated serine protease, namely MASP-1 and MASP-2. Endo et al investigated whether the lectin pathway was involved in the pathogenic mechanism of IgA-N. Endo uses monoclonal antibodies against MBL and MASP-1 to do immunohistochemical study on forty-five renal biopsy cases with IgA-N, 35 cases with other forms of glomerulonephritis (GN). Endo et al teach that glomerular deposition of MBL, which was accompanied by MASP-1, was detected in 11 of 45 (24.4%) with IgA-N, while it was detected in only one case with other forms of GN. The deposited MBL/MASP-1 was observed to associate with C3b/C3c and C5b-9 but not with IgG, IgM, C1q, C4c or properdin. Compared with MBL/MASP-1 negative cases with IgA-N, the positive cases with IgA-N were young and the renal biopsies had been performed at an early stage of the disease. Endo et al concluded that the lectin pathway of complement activation, which is initiated by the MBL/MASPs complex, evidently contributes to the development of glomerular injury in a significant number of cases with IgA-N. In addition, these findings will add insight to the pathogenesis of IgA-N, including its relation to infection, since MBL plays a crucial role in the host defense against various pathogens (see abstract, page 1984, 2nd col., 1st ¶). Endo et al teach that a deeper understanding of the mechanism of complement activation in IgA-N may help to elucidate the pathogenesis, since it is apparent that

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the complement system participates in the development of the disease. Endo et al teach that their finding suggest that the lectin pathway, which is initiated by MBL/MASPs complex, is a certain mechanism of activating the complement cascade in IgA-N. The deposition of MBL/MASP-1, in addition, was concordant with the presence of C3b/C3c and C5b-9, which indicated the occurrence of on-going complement activation *in situ* (see page 1987, under Discussion). Endo et al teach that these findings suggest that the lectin pathway participates in the development of the disease at an early stage in consideration of the result that none of the cases with MBL/MASP-1 deposition had advanced histological alteration. Taking the time of biopsy into account, the prevalence of glomerular C3 deposits may be caused by complement activation predominantly via the lectin pathway.

The claimed invention differs from the reference teachings only by the recitation of inhibiting LCP associated complement activation with MBL inhibitor such as antibody in claims 1, 25, 40, 53, 70, wherein in the inhibitor binds a mammalian cell with a surface exposed MBL ligand in claims 12 and 50, and wherein the antibody is monoclonal antibody in claims 26, 35 and 71, wherein the MBL inhibitor binds MBL in claims and 51, wherein the MBL inhibitor binds to a human MBL epitope in claims 13 and 57.

Base on the observation that glomerular deposition of MBL, which was accompanied by MASP-1, in association with C3b/C3c and C5b-9, indicates complement activation in IgA nephropathy. This suggests that lectin pathway participates in the development of the IgA nephropathy disease. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made would be motivated to therapeutic target the formation of MBL/MASPs complex taught by Endo et al with MBL inhibitor such as monoclonal antibodies against MBL or MASP-1 taught by Endo et al for the treatment/inhibition the initiation of MBL/MASPs complex and prevent the development of glomerular injury. One of ordinary skill in the art would have had a reasonable expectation of success of inhibiting LCP associated complement activation mediated IgA nephropathy according to the teachings of Endo et al by providing an anti-MBL antibody or anti-MASP-1 to a patient suffering from this disease inasmuch as the reference discloses that the lectin pathway is initiated intermittently by MBL/MASPs complex and serves as a trigger for the activation of the amplification cycle via the alternative pathway and that this initiation is associated with repeated antigen exposures such as infection and it discloses specific examples of such anti-MBL antibodies and anti-MASPs antibodies.

The claimed function limitations would be expected properties as a result of the inhibition with the MBL inhibitors.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

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16. Claims 1-2, 6, 12, 13, 15, 25, 26, 30-33, 35, 38, 40, 44, 50, 51, 53, 56, 57, 60-63, 70-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malhotra et al (Nat Med. 1995 (3):237-43) in view of Endo et al (Nephrol Dial Transplant. 1998 Aug;13(8):1984-90, IDS C13).

Malhotra et al teach mannose binding lectin (MBL, MBP) upon binding to the specific carbohydrate, its associated serine proteases (MBL associated serine proteases or MASP) get activated leading to activation of complement cascade; lectin pathway. Consequently it has significant role in eliciting the inflammatory response and thus it has been well associated with the pathogenesis of rheumatoid arthritis. Particularly in RA, agalactosylated IgG (IgG0) that has an exposed GlcNAc can be an easy target for MBL binding leading to generation of inflammatory response. Malhotra et al demonstrate that the alteration in glycosylation associated with rheumatoid arthritis can create a new mode for the interaction of IgG with complement through binding to the collagenous lectin mannose-binding protein (see abstract and page 240, bridging ¶ between col., 1 and 2).

The claimed invention differs from the reference teachings only by the recitation of inhibiting LCP associated complement activation with MBL inhibitor such as antibody in claims 1, 25, 40, 53, 70, wherein in the inhibitor binds a mammalian cell with a surface exposed MBL ligand in claims 12 and 50, and wherein the antibody is monoclonal antibody in claims 26, 35 and 71, wherein the MBL inhibitor binds MBL in claims and 51, wherein the MBL inhibitor binds to a human MBL epitope in claims 13 and 57.

The teachings of Endo et al have been discussed, supra. In particular, Endo et al teach both monoclonal antibody against MBL and MASP-1 (see abstract).

Base on the observation that the occurrence of MBP in synovial fluid coupled with the presence of high levels of IgG-G0 structures leading to generation of inflammatory response of the synovial membrane of affected joints. This suggests that lectin pathway participates in the development of rheumatoid arthritis. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made would be motivated to therapeutic target the formation of MBL/IgG0 complex taught by Malhotra et al with MBL inhibitor such as monoclonal antibodies against MBL taught by Endo et al for the treatment/inhibition the initiation of MBL/IgG0 complex and prevent the development of rheumatoid arthritis. One of ordinary skill in the art would have had a reasonable expectation of success of inhibiting LCP associated complement activation mediated rheumatoid arthritis according to the teachings of Malhotra et al by providing an anti-MBL antibody or anti-MASP-1 taught by Endo et al to a patient suffering from rheumatoid arthritis disease inasmuch as the Malhotra reference discloses that the lectin pathway is initiated by MBL/IgG0 complex results in activation of the complement that contributes to the chronic inflammation of the synovial membrane, which arise from the localization (deposition) of the IgG-G0 on the affected joint from the resulting activation of complement and it discloses specific examples of such anti-MBL antibodies and anti-MASPs antibodies.

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The claimed function limitations would be expected properties as a result of the inhibition with the MBL inhibitors.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 1-2, 6, 12, 13, 15, 25, 26, 30-33, 35, 38, 40, 44, 50, 51, 53, 56, 57, 60-63, 70-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuda et al., (Journal of Nephrology Association of Japan, 39(3): 235 (1997)), optionally in view of Endo et al (Nephrol Dial Transplant. 1998 Aug;13(8):1984-90, IDS C13).

Matsuda et al teach that mannan-binding protein (MBP) is a lectin which binds specifically to the sugar chains such as N- acetylglucosamine and mannose, and activates complement activity via lectin pathway different from classical and alternative pathways. Recently, abnormal structures of sugar chains type of IgA have been reported in the patients with nephropathy, and the sugar chains with binding ability to MBP were included among them. Matsuda et al examined localization and significance of MBP in glomerulus of the patients with IgA nephropathy. Matsuda et al teach the localizations of MBP and various complement components were immunohistologically (using antibodies to MBP) examined using frozen sections of renal biopsy specimens obtained from patients with IgA nephropathy, membranous nephropathy, lupus nephropathy, and microvariant nephrotic syndrome. Additionally, the correlation of MBP deposition with renal tissue findings and clinical laboratory data were examined. Deposition of MBP in glomerulus was observed in approximately 10% of patients with IgA nephropathy. Higher frequencies of C2 and C4 staining in glomerulus were found in MBP-positive compared to MBP-negative patients with IgA nephropathy. Lower renal functions and tendency of more proteinuria were observed in MBP-positive cases. Matsuda et al teach that deposition of MBP in glomerulus was observed in some cases of IgA nephropathy, suggesting that complement activation via lectin pathway in addition to alternative pathway might be involved in incidence of IgA nephropathy. The tendency of higher renal dysfunction was observed in MBP- positive cases (see English translation of the Abstract).

The claimed invention differs from the reference teachings only by the recitation of inhibiting LCP associated complement activation with MBL inhibitor such as antibody in claims 1, 25, 40, 53, 70, wherein in the inhibitor binds a mammalian cell with a surface exposed MBL ligand in claims 12 and 50, and wherein the antibody is monoclonal antibody in claims 26, 35 and 71, wherein the MBL inhibitor binds MBL in claims and 51, wherein the MBL inhibitor binds to a human MBL epitope in claims 13 and 57.

The teachings of Endo et al have been discussed, supra. In particular, Endo et al teach both monoclonal antibody against MBL and MASP-1 (see abstract).

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Base on the observation that tendency of higher renal dysfunction was observed in MBP-positive cases, and higher frequencies of C2 and C4 staining in glomerulus were found in MBP-positive compared to MBP-negative patients with IgA nephropathy. This suggests that involvement of MBP in incidence and development of IgA nephropathy. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made would be motivated to therapeutic target MBP taught by Matsuda et al with MBL inhibitor such as monoclonal antibodies against MBL taught by Matsuda et al or Endo et al for the treatment/inhibition of MBP and prevent the development of IgA nephropathy. One of ordinary skill in the art would have had a reasonable expectation of success of inhibiting LCP associated complement activation mediated IgA nephropathy according to the teachings of Matsuda et al by providing an anti-MBL antibody or anti-MASP-1 taught by Matsuda et al or Endo et al to a patient suffering from IgA nephropathy disease inasmuch as the Matsuda reference discloses that the tendency of higher renal dysfunction was observed in MBP-positive cases and it discloses specific examples of such anti-MBL antibodies.

The claimed function limitations would be expected properties as a result of the inhibition with the MBL inhibitors.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. Claims 22-23, 25-26, 28-29, 36-37, 54-55, 67-68 and 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Endo et al (Nephrol Dial Transplant. 1998 Aug;13(8):1984-90, IDS C13) as applied to claims 1, 13, 33, 40, 51 and 70 and further in view of Owens *et al* (1994).

The teachings of Endo et al reference have been discussed, *supra*.

The claimed invention differs from the reference teaching only by the recitation of a single chain antibody, a Fab fragment, a F(ab')₂ fragment or a humanized antibody.

Owens *et al* teach the modification of murine antibodies such as a single chain antibody, a Fab fragment, a F(ab')₂ fragment or a humanized antibody antibodies monoclonal antibody technology, single chain, Fab fragments, and F(ab')₂. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement –dependent cytotoxicity (see the entire document).

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Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the antibody taught by Endo et al as humanized antibody, Fab and F(ab')₂ fragments taught by the Owens *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications as taught by Owens *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claims 22-23, 25-26, 28-29, 36-37, 54-55, 67-68 and 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malhotra et al (Nat Med. 1995 (3):237-43) in view of Endo et al (Nephrol Dial Transplant. 1998 Aug;13(8):1984-90, IDS C13) as applied to claims 1, 13, 33, 40, 51 and 70 and further in view of Owens *et al* (1994).

The teachings of Malhotra et al and Endo et al reference have been discussed, *supra*.

The claimed invention differs from the reference teaching only by the recitation of a single chain antibody, a Fab fragment, a F(ab')₂ fragment or a humanized antibody.

Owens *et al* teach the modification of murine antibodies such as a single chain antibody, a Fab fragment, a F(ab')₂ fragment or a humanized antibody antibodies monoclonal antibody technology, single chain, Fab fragments, and F(ab')₂. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement –dependent cytotoxicity (see the entire document).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the antibody taught by Endo et al as humanized antibody, Fab and F(ab')₂ fragments taught by the Owens *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications as taught by Owens *et al*.

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From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claims 22-23, 25-26, 28-29, 36-37, 54-55, 67-68 and 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuda et al., (Journal of Nephrology Association of Japan, 39(3): 235 (1997)), optionally in view of Endo et al (Nephrol Dial Transplant. 1998 Aug;13(8):1984-90, IDS C13), as applied to claims 1, 13, 33, 40, 51 and 70 and further in view of Owens *et al* (1994).

The teachings of Matsuda et al and Endo et al reference have been discussed, *supra*.

The claimed invention differs from the reference teaching only by the recitation of a single chain antibody, a Fab fragment, a F(ab')₂ fragment or a humanized antibody.

Owens *et al* teach the modification of murine antibodies such as a single chain antibody, a Fab fragment, a F(ab')₂ fragment or a humanized antibody antibodies monoclonal antibody technology, single chain, Fab fragments, and F(ab')₂. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement –dependent cytotoxicity (see the entire document).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the antibody taught by Matsuda et al or Endo et al as humanized antibody, Fab and F(ab')₂ fragments taught by the Owens *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications as taught by Owens *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

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20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

April 27, 2010

/Maher M. Haddad/
Primary Examiner,
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